REMARKS

1. Rejection of Claims 1, 3-5, 7-9, 11-13, 15-17, 19-21, 23-25, 27-29, 31-33 and 35-36 under 35 U.S.C. 112, first paragraph.

Claims 1, 3-5, 7-9, 11-13, 15-17, 19-21, 23-25, 27-29, 31-33 and 35-36 were rejected under 35 U.S.C. 112, first paragraph as allegedly failing to enable estradiol metabolites other than 2HE, 2ME, 4HE and 4ME, for the reasons of record. In particular, the Examiner argued that the specification fails to provide information that would allow one of skill in the art to practice the claimed invention without undue experimentation, citing the 8 factors set forth by *In re Wands*.

Initially, Applicants note that claims have been amended as set forth above to recite an estradiol metabolite selected from the group consisting of a catecholestradiol and a methoxyestradiol. Applicants also note that the specification defines "estradiol" as 17.beta.-estradiol and "estradiol metabolite(s)" as metabolites of 17.beta.-estradiol and thus the claims are directed to compounds having clear structural features and defined properties, such as exerting little estrogenic activity and having a low affinity for the estrogen receptor.

Nonetheless, Applicants respectfully traverse the Examiner's rejection. Applicants direct the Examiner's attention to cases that established the groundwork for the *In re Wands* test, such as *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). In that case the inventors appealed a board decision holding undue experimentation would be required to determine which of thousands of possible combinations would work to produce hydroperoxides in their claimed catalytic process. First, the court determined that the claimed process was an "unpredictable" art. The dissent argued that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty*

before performing the reaction, whether the claimed product will be obtained" (emphasis in original) *In re Angstadt*, 190 USPQ at 222. The majority rejected this approach, arguing that under the dissent's standard, "all 'experimentation' is 'undue' since the term 'experimentation' implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the Patent Act", *In re Angstadt*, 190 USPQ at 219. The majority continued, "What the dissent seems to be obsessed with is the thought of catalysts which *won't* work to produce the intended result. Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." (emphasis in original), *In re Angstadt*, 190 USPQ at 219.

The Court of Appeals for the Federal Circuit (CAFC) has upheld the holding of *In re Angstadt* on many occasions post establishing the *In re Wands* test, including in biotechnology cases. For example, in *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ 1016, 1027 (CAFC 1991) the court cited *In re Angstadt* as standing for the proposition that "it is not necessary that a patent applicant test all the embodiments of his invention".

Applying the reasoning of the majority of *In re Angstadt* to the present application, Applicants respectfully argue that 35 U.S.C. 112 does not require the specification to set forth teachings in order to guide one of skill in the art on how to practice all possible embodiments or to predict which compounds will work. Rather, what is required is that one of skill in the art must have sufficient guidance to be able to determine whether or not a given compound falls within the scope of the claim. Applicants argue that this can be readily accomplished by determining if the compound in question has a structure consistent with being a catecholestradiol or methoxyestradiol metabolite 17.beta.-estradiol, the structure of which is

known to those of skill in the art. That is, Applicants assert that given the teachings of the present application, determining whether a given compound falls within the claims is a matter of routine screening. See *In re Wands* 8 USPQ2d 1400, 1404 in which the court held routine screening does not constitute undue experimentation.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Claims 1, 3-5, 7-9, 11-13, 15-17, 19-21, 23-25, 27-29, 31-33 and 35-36 under 35 U.S.C. 112, first paragraph.

2. Rejection of Claims 3, 7, 11, 15, 19, 23, 27, 31 and 35 under 35 U.S.C. 112, second paragraph.

Claims 3, 7, 11, 15, 19, 23, 27, 31 and 35 were rejected under 35 U.S.C. 112, second paragraph for the reasons of record. Specifically, the Examiner argued that the limitation of "prodrug of estradiol metabolite" renders the claim indefinite because it is not clear what compounds are encompassed by the claims.

Applicants respectfully traverse the Examiner's rejection. Initially, Applicants note that the specification defines a prodrug as a compound that releases an estradiol metabolite. Applicants are entitled to rely upon the ordinary and common usage of terms well known to those of skill in the art. Applicants respectfully argue that the term "prodrug" is commonly understood by those of skill in the art to be a drug construct in which one or more structures are added to a base drug to inactivate the drug and the drug becomes active when such structures are removed, such as by metabolic processes. As such, the term "prodrug" has a definite meaning to one of skill in the art and meets the requirements of 35 U.S.C. 112, second paragraph.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Claims 3, 7, 11, 15, 19, 23, 27, 31 and 35 under 35 U.S.C. 112, second paragraph.

3. Rejection of Claims 1-36 under 35 U.S.C. 103(a)

Claims 1-36 were rejected under 35 U.S.C. 103(a) as obvious over Chwalisz et al. and Parker et al. in view of Xiao et al., for the reasons of record.

Initially, Applicants respectfully assert that the office action mis-characterizes disclosure of Xiao et al. The Xiao et al reference teaches that estradiol, but not 2ME or 2HE, increases nitric oxide (see Xiao et al. Figure 1). Accordingly, Xiao et al teaches that estradiol metabolites such as 2ME and 2HE would not be effective in a nitric oxide deficiency disease such as pulmonary hypertension.

The primary references Parker et al and Chwalisz et al each teach that estradiol is beneficial in treating pulmonary hypertension via increasing nitric oxide. Accordingly, the combination of either of the primary references with Xiao et al teaches away from the present invention because Xiao et al. teaches that estradiol metabolites such as 2ME and 2HE are not effective in increasing nitric oxide. Accordingly, one of skill in the art would have neither motivation nor a reasonable expectation of success that estradiol metabolites would be useful in the treatment of a nitric oxide deficiency disease and the combined references fail to teach or suggest every element of the claimed invention as required for a rejection under 35 U.S.C. 103(a).

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Claims 1-36 under 35 U.S.C. 103(a).

In view of the foregoing, Applicants respectfully submit that all rejections under 35 U.S.C. 112 and 35 U.S.C. 103(a) have been overcome. Accordingly, Applicants believe that Claims 1-36 are in condition for allowance.

Respectfully Submitted,

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